

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
12 August 2004 (12.08.2004)

PCT

(10) International Publication Number
WO 2004/066997 A3

(51) International Patent Classification⁷: **A61K 31/4178**,
A61P 9/12, C07D 403/10

(21) International Application Number:
PCT/SI2004/000001

(22) International Filing Date: 29 January 2004 (29.01.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

| | | |
|-------------|------------------------------|----|
| P-200300026 | 30 January 2003 (30.01.2003) | SI |
| P-200300025 | 30 January 2003 (30.01.2003) | SI |
| P-200300145 | 12 June 2003 (12.06.2003) | SI |
| P-200300157 | 26 June 2003 (26.06.2003) | SI |
| P-200300270 | 5 November 2003 (05.11.2003) | SI |

(71) Applicant (for all designated States except US): **LEK
PHARMACEUTICALS D.D.** [SI/SI]; Verovskova 57,
1526 Ljubljana (SI).

(72) Inventors; and

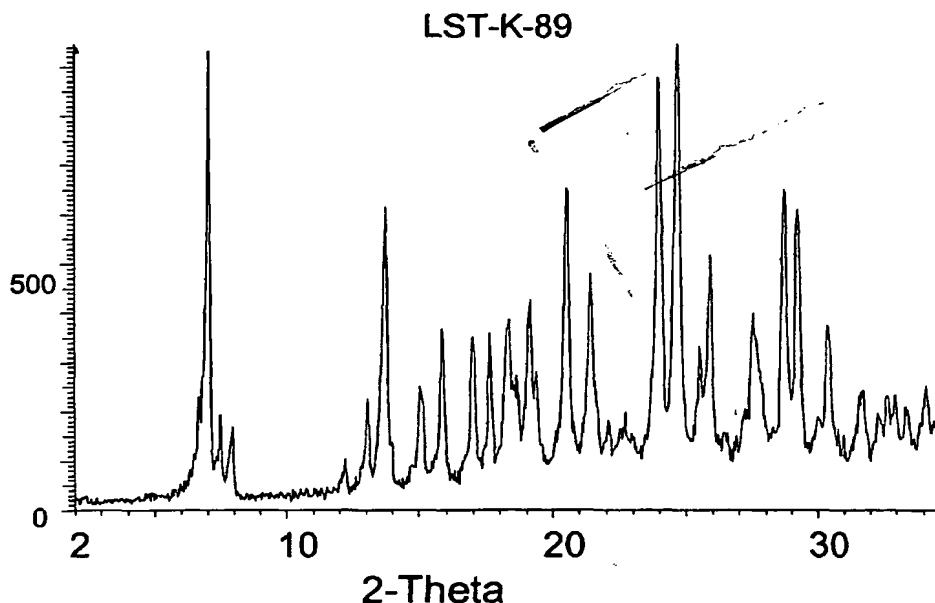
(75) Inventors/Applicants (for US only): **ANTONCIC**,
Ljubomir [SI/SI]; Podmiljsakova 43, Ljubljana (SI).
COPAR, Anton [SI/SI]; Stareto trg 1, 1275 Smartno pri
Litiji (SI). **SVETE, Peter** [SI/SI]; Gradisnikova 14, 1353
Borovnica (SI). **HUSU-KOVACECIC, Breda** [SI/SI]; Na
Peci 27, 1000 Ljubljana (SI). **HAM, Zoran** [SI/SI]; Trg
Franca Fakina 7, 1420 Trbovlje (SI). **MAROLT, Boris**
[SI/SI]; Presernova 7, 1236 Trzin (SI).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,

[Continued on next page]

(54) Title: PREPARATION OF NEW PHARMACEUTICALLY SUITABLE SALT OF LOSARTAN AND FORMS THEREOF
WITH NEW PURIFICATION AND ISOLATION METHODS



(57) Abstract: Pharmaceutically suitable crystalline and amorphous alkali and earth-alkali salts of 2-n-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1 H-tetrazole-5-yl)[1.1'-biphenyl]-4-yl]-1-imidazole have been prepared and new manufacturing, purification and isolation procedure for said salts in high purity have been described. Stable pharmaceutical compositions containing new crystalline potassium salts of 2-n-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1 H-tetrazole-5-yl)[1.1'-biphenyl]-4-yl]-1-imidazole have been prepared.

BEST AVAILABLE COPY

WO 2004/066997 A3



GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) **Date of publication of the international search report:**

11 November 2004

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PC 2004/000001

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4178 A61P9/12 C07D403/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | US 5 962 500 A (KJELDSSEN SVERRE E ET AL) 5 October 1999 (1999-10-05) column 16, line 14 - line 22; example 1 column 16, line 37 column 16, line 30 - line 37 column 26, line 1 - line 4 | 1,8 |
| X | EP 1 106 611 A (SUMIKA FINE CHEMICALS CO LTD) 13 June 2001 (2001-06-13) cited in the application page 4, line 20 - line 21 | 1,8 |
| X | US 5 795 904 A (COHEN SHEILA M ET AL) 18 August 1998 (1998-08-18) column 9, line 35 - line 37; claim 1 | 1,8 |
| | -/-- | |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

17 June 2004

Date of mailing of the international search report

08. 09. 2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Härtinger, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/0004/000001

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | WO 97/00070 A (PETTERSSON ANDERS ; ASTRA AB (SE); FAENDRIKS LARS (SE)) 3 January 1997 (1997-01-03) *formula I:1* page 4, line 5 - line 7 ----- | 1,8 |
| P,X | WO 03/035039 A (DEPOMED INC) 1 May 2003 (2003-05-01) page 4, line 4 - line 9 ----- | 1,8 |

BEST AVAILABLE COPY

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SI2004/000001

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1,8 (part)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1,8(part)

Earth-alkali salts of losartan

2. claims: 2,8(part),9

Sodium salts of losartan

3. claims: 7,17-21,24,25(part)

Amorphous alkali or earth-alkali salts of losartan

4. claims: 10,11

Process for purification of losartan comprising the use of any salt of losartan

5. claims: 3,6(part),12-14,22,23(part),25(part),26-27,28(part)

Crystalline losartan K-salt hydrate

6. claims: 4,6(part),15-16(part),22,25(part),26-28(part)

Crystalline K-salt form X

7. claims: 5,6(part),15-16(part),22-23(part),25(part),26-28(part)

Crystalline K-salt form Y

8. claim: 28

Pharmaceutical composition comprising any losartan K-salt incrySTALLINE form

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/004/000001

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|--|--|
| US 5962500 | A | 05-10-1999 | AU 2225395 A WO 9526724 A1 | 23-10-1995 12-10-1995 |
| EP 1106611 | A | 13-06-2001 | JP 2001226372 A AT 269858 T DE 60011739 D1 EP 1106611 A1 US 6350880 B1 | 21-08-2001 15-07-2004 29-07-2004 13-06-2001 26-02-2002 |
| US 5795904 | A | 18-08-1998 | NONE | |
| WO 9700070 | A | 03-01-1997 | AT 214925 T AU 706660 B2 AU 1184097 A BR 9608472 A CA 2225175 A1 CN 1192681 A , B CZ 9703730 A3 DE 69620186 D1 DE 69620186 T2 DK 840607 T3 EE 9700366 A EP 0840607 A1 ES 2173294 T3 HK 1010152 A1 HU 9901448 A2 IL 122659 A JP 11507921 T NO 975922 A NZ 310606 A PT 840607 T RU 2209064 C2 WO 9700070 A1 SK 172197 A3 US 6096772 A ZA 9604690 A | 15-04-2002 17-06-1999 15-01-1997 29-12-1998 03-01-1997 09-09-1998 13-05-1998 02-05-2002 31-10-2002 06-05-2002 15-06-1998 13-05-1998 16-10-2002 19-07-2002 28-04-2000 12-01-2003 13-07-1999 16-12-1997 30-03-2001 30-09-2002 27-07-2003 03-01-1997 08-07-1998 01-08-2000 19-12-1996 |
| WO 03035039 | A | 01-05-2003 | CA 2464561 A1 EP 1438027 A1 WO 03035039 A1 US 2003158244 A1 | 01-05-2003 21-07-2004 01-05-2003 21-08-2003 |

BEST AVAILABLE COPY